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The Impact of Demographic, Social, and Environmental Factors on the Development of Steroid-Responsive Meningitis-Arteritis (SRMA) in the United Kingdom

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Background: Steroid-responsive meningitis-arteritis (SRMA) is an inflammatory disease of dogs that is suspected to be immune-mediated. The development of other immune-mediated diseases has been linked to vaccinations, time of the year, geographic location, sex, neuter status, and breed.

Hypothesis/Objectives: To identify if the development of SRMA is associated with time of year, vaccination, geographic location, sex, neuter status, and breed.

Animals: Sixty SRMA cases and 180 controls, all ≤24 months of age and matched for year of presentation, from a referral hospital population in the United Kingdom.

Methods: Retrospective case-control study with unconditional logistic regression analysis.

Results: Beagles ($P = .001$), Border Collies ($P = .001$), Boxers ($P = .032$), Jack Russell Terriers ($P = .001$), Weimaraners ($P = .048$), and Whippets ($P < .001$) had significantly greater odds of developing SRMA in this population of dogs. Vaccination, time of year, geographic category, sex, and neuter status did not increase the odds of developing SRMA.

Conclusions and Clinical Importance: Only breed increased the odds of developing SRMA. It would be prudent to investigate the genetics of the identified breeds to help elucidate the etiopathogenesis of SRMA.

Key words: Aseptic meningitis; Necrotizing vasculitis.

Steroid-responsive meningitis-arteritis (SRMA) is a well-recognized inflammatory disease of dogs. One study documented a prevalence of 0.6% of all cases and 1.6% of neurologic consults at a referral hospital in the United Kingdom.[1]

SRMA can occur in any breed but Beagles, Boxers, Bernese Mountain Dogs (BMD), Nova Scotia Duck Tolling Retrievers (NSDTR), Weimaraners, and English Springer Spaniels[1,2] seem to be predisposed. No sex predisposition exists for the disease. The age of onset of SRMA is 3 months to 9 years, but 1 study suggested resistance to relapse develops at approximately 2 years of age.[3]

Dogs with SRMA have a waxing and waning disease course characterized by episodic cervical hyperesthesia, obtundation, and pyrexia.[2] Acute and chronic forms of the disease exist.[2] There is no definitive antemortem test for SRMA and diagnosis is based on clinical criteria, laboratory findings, exclusion of other diseases,[1] and response to corticosteroids.

The etiopathogenesis of SRMA is unknown, but an immune-mediated process is suspected.[2] An antigenic stimulus is suspected to trigger SRMA but no infectious or neoplastic triggers have been identified.[2,3]

Abbreviations:

BMD	Bernese Mountain Dogs
CSF	cerebrospinal fluid
IMHA	immune-mediated hemolytic anemia
IMTP	immune-mediated thrombocytopenia
JRT	Jack Russell terriers
MHC II	major histocompatibility complexes class II molecule
NSDTR	Nova Scotia Duck Tolling Retrievers
OR	odds ratio
SRMA	steroid-responsive meningitis-arteritis
TNCC	total nucleated cell count

Antigenic triggers have been identified for other immune-mediated diseases, and infections, neoplasms, drugs, and vaccinations have been implicated.[4]

The prevalence of some immune-mediated diseases in dogs has been associated with time of year, breed, sex, and neuter status.[4] In humans, immune-mediated conditions have been shown to have associations with social factors, including geographic location.

The aim of this study was to determine if development of SRMA was associated with time of year, vaccination, geographic location, sex, neuter status, or breed. These results may identify factors for further investigation that could help elucidate the etiopathogenesis of SRMA.

Materials and Methods

Dogs with the acute form of SRMA were identified by searching records of cases presented to Langford Veterinary Services between January 1, 2003, and December 31, 2012. Cases were included if they had neck pain, obtundation, pyrexia, a cisternal cerebrospinal fluid (CSF) sample with neutrophilic pleocytosis and no pathologic organisms on cytology, a CBC and serum biochemistry profile, normal orthogonal cervical radiographic findings, and resolution of clinical signs after treatment with corticosteroids. Cases were excluded if they had neurologic deficits

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in addition to neck pain and obtundation or if they were over 24 months of age at presentation.

Neck pain was defined by a behavioral change or resistance to movement when the cervical spine was manipulated laterally or vertically. Obtundation was defined as decreased response to environmental stimuli. Pyrexia was defined as a rectal temperature >102.5°F. Neutrophilic pleocytosis in CSF was defined as a total nucleated cell count (TNCC) >5 cells/μL and total protein >25 mg/dL with >50% of the TNCC being neutrophils.

Three controls, matched for year of presentation, were selected per SRMA case.[5] Hospital numbers of controls were randomly selected by using a computer program.[a] Patients were selected as controls if they were dogs ≤24 months of age, had been referred with clinical signs indicative of a pathologic process, had not been diagnosed with SRMA, or if no diagnosis had been made, did not have signs of neck pain, obtundation, or pyrexia. If the selected patient failed to meet these criteria, the ascending and then descending sequential hospital number was reviewed until a control was identified.

Information regarding the date of onset of disease, time between last vaccination and onset of disease, postal code, sex, neuter status, and breed was recorded for all cases and controls.

The date of onset of disease was categorized by season: Spring (March, April, and May), Summer (June, July, and August), Autumn (September, October, and November), or Winter (December, January, and February).

Time from vaccination to onset of disease was categorized as ≤6 weeks or >6 weeks. This time frame is commonly used when investigating the association between vaccination and Guillain-Barré syndrome.

Each postal code was used to generate metadata about urban or rural indicators based on UK Census data.[b] Cases and controls were assigned to 1 of 4 environmental categories: urban, town and fringe, village, and hamlet with isolated dwelling.

Individual breeds were analyzed if they occurred at a frequency ≥3 in the SRMA dataset or had been reported previously to have an increased incidence of SRMA in other studies. All other breeds were placed in 1 category labeled "other breeds."

Normality was tested in cases and controls on age at onset of disease by using a Shapiro-Wilk test with a software program.[c] An unpaired 2-tailed *t*-test was performed to compare the age at onset of disease between cases and controls by using a software program.[d]

Univariable unconditional logistic regression analysis was performed on the dataset for the variables season, vaccination date, environmental category, sex, neuter status, and breed by using a software program.[c] Variables with a univariable $P < .2$ were considered for inclusion in a multivariable model to allow for possible confounding. Variables with a $P < .05$ in the multivariable model were considered significant.

Results

Sixty SRMA cases met the inclusion and exclusion criteria and therefore 180 controls were selected. SRMA cases made up 0.37% of dogs referred to our clinic (2003–2012).

The age of onset of disease data were normally distributed (Shapiro-Wilk, $P < .001$). The mean (standard deviation) was 10.25 months (5.02) for SRMA cases and 9.51 months (6.86) for controls. The means for these groups were not significantly different ($P = .44$). Univariable unconditional logistic regression did not show significantly increased odds of developing SRMA with the variables of season, vaccination date, environmental category, or sex (Table 1). Multivariable unconditional logistic regression showed Beagles, Border collies, Boxers, Jack Russell Terriers (JRT), Weimaraners, and Whippets had significantly increased odds of developing SRMA compared to "other breeds." Neuter status did not have a significant effect on the odds of developing SRMA (Table 1).

Discussion

The odds of developing SRMA were significantly increased for Beagles, Border Collies, Boxers, JRT, Weimaraners, and Whippets in this population of dogs. No other associations, including time of year, vaccination, geographic location, sex, and neuter status, were found. Other breeds may have an increased probability of developing SRMA that was not identified in this study, because of type 2 statistical error, associated with the limited number of dogs in this investigated population.

Beagles and Weimaraners previously have been reported to be overrepresented in studies of SRMA,[2] whereas Boxers have been statistically proven to be overrepresented.[1] Our study supports these findings. Jack Russell Terriers, Border Collies, and Whippets have not previously been shown to be overrepresented or to have increased odds of developing SRMA. These breeds may be kept by owners whose lifestyle exposes the dogs to an environmental trigger, or they may have a genetic predisposition to develop SRMA that was not previously identified because of smaller study sizes. There is evidence to suggest a genetic predisposition to various immune-mediated diseases in dogs. For example, some breeds may be predisposed to hypoadrenocorticism secondary to a mutation in genes associated with the major histocompatability complex class II molecule (MHC II).[6,7] Given the link between MHC II and activated T cells[8] and the presence of activated T cells in SRMA,[2] it may be worth investigating this link in the breeds with increased odds of developing SRMA.

We did not demonstrate increased odds of developing SRMA in English Springer Spaniels, but another study has statistically shown overrepresentation of this breed.[1] Nor did our study show any increased odds for BMD and NSDTR to develop SRMA, although overrepresentation of these breeds has been suspected.[2] This may represent a geographic variation in intrabreed susceptibility to SRMA, a variation in breed popularity with location such that environmental factors may be influential, or type 2 statistical error.

Bitches and neutered dogs have been shown to be more susceptible to immune-mediated hemolytic anemia (IMHA)[4] and immune-mediated thrombocytopenia (IMTP), leading to the hypothesis that androgen hormones may be protective against immune-mediated disease development. Sex and neuter status did not significantly affect the odds of developing SRMA in our study. Previous studies also have shown no relation of sex to SRMA, making androgens unlikely to be protective against SRMA.

Table 1. Results of univariable and multivariable analysis.

Variable	SRMA Cases (n)	Controls (n)	OR	95% CI	*P*-Value
Univariable analysis					
Season					.78
Spring	18 (30%)	43 (24%)	1.00		
Summer	12 (20%)	40 (22%)	0.72	0.31–1.67	.44
Autumn	16 (27%)	47 (26%)	0.81	0.37–1.79	.61
Winter	14 (23%)	50 (28%)	0.67	0.30–1.50	.33
Vaccination to onset of disease					
<42 days	10 (17%)	38 (21%)	1.00		
>42 days	50 (83%)	142 (79%)	1.34	0.62–2.88	.46
Environmental category					
Urban	37 (62%)	97 (54%)	1.00		.77
Town	8 (13%)	29 (16%)	0.72	0.30–1.73	.47
Village	9 (15%)	31 (17%)	0.76	0.33–1.75	.52
Hamlet	6 (10%)	23 (13%)	0.68	0.26–1.81	.45
Sex					
Male	34 (57%)	100 (56%)	1.00		
Female	26 (43%)	80 (44%)	0.96	0.53–1.72	.88
Neutering status					
Entire	39 (65%)	133 (74%)	1.00		
Neutered	21 (35%)	47 (26%)	1.52	0.82–2.85	.19
Breed					<.001
Other breeds	21 (35%)	145 (81%)	1.00		
Beagle	5 (8%)	3 (2%)	11.51	2.56–51.72	.001
Border Collies	7 (12%)	7 (4%)	6.91	2.20–21.66	.001
Boxers	4 (7%)	6 (3%)	4.60	1.20–17.67	.026
JRT	7 (12%)	7 (4%)	6.91	2.20–21.66	.001
Weimaraners	2 (3%)	1 (1%)	13.81	1.20–159.02	.035
Whippets	11 (18%)	2 (1%)	37.98	7.86–183.38	<.001
BMD	0 (0%)	1 (1%)	0.00	0.00–	1.00
English Springer Spaniels	2 (3%)	8 (4%)	1.73	0.34–8.69	.51
NSDTR	1 (2%)	0 (0%)	11150000000.00	0.00–	1.00
Multivariable analysis					
Neutering status					
Entire	39 (65%)	133 (74%)	1.00		
Neutered	21 (35%)	47 (26%)	1.44	0.69–2.99	.33
Breed					<.001
Other breeds	21 (35%)	145 (81%)	1.00		
Beagle	5 (8%)	3 (2%)	11.67	2.58–52.72	.001
Border Collies	7 (12%)	7 (4%)	6.54	2.07–20.67	.001
Boxers	4 (7%)	6 (3%)	4.39	1.14–16.98	.032
JRT	7 (12%)	7 (4%)	6.54	2.07–20.67	.001
Weimaraners	2 (3%)	1 (1%)	12.04	1.03–141.55	.048
Whippets	11 (18%)	2 (1%)	38.97	8.03–189.03	<.001
BMD	0 (0%)	1 (1%)	0.00	0.00–	1.00
English Springer Spaniels	2 (3%)	8 (4%)	1.77	0.35–8.92	.49
NSDTR	1 (2%)	0 (0%)	12354280409.00	0.00–	1.00

n, number; OR, odds ratio; CI, confidence interval.

In IMHA and IMTP, an association between time of year and onset of disease has been reported,[4] leading to the suggestion that time of year may be linked to exposure to infectious agents that trigger disease. This finding has not been replicated in other studies of IMHA or immune-mediated polyarthritis. There was no increase in odds of developing SRMA in any season in our study suggesting that if an infectious trigger exists for SRMA, its exposure is not influenced by season in the South West United Kingdom.

Links between immune-mediated diseases and vaccination have been made, but controversy surrounds this association.[4] Vaccination within 6 weeks of the onset of SRMA was not found to increase the odds of developing the disease in our study, suggesting vaccination is unlikely to trigger SRMA.

There is some evidence that geographic factors can affect immune-mediated disease prevalence in humans by influencing exposure to microbial agents, diet, and stress. In dogs, geographic location can affect exposure to microbial agents such as ticks and leptospirosis.[9,10] No increased probability was shown for environmental category and SRMA in our study. There still could be a link between geographic location and SRMA because we may have investigated the wrong factors and those that live in urban environments may travel

to exercise their dogs. We have not examined the United Kingdom as a whole and it may be that dogs in particular sections of the country are prone to SRMA. As such, it could be important to investigate this possibility more extensively in the future.

The main limitation of this article was the number of SRMA cases. To our knowledge, this number exceeds the number of cases in any other published study, but it limited the power of the study to detect variables with small effect sizes on the odds of developing SRMA. By using a posthoc power calculation with a confidence interval of 95%, power 80%, and exposure of control to the variables under investigation at 25% (selected given the assumption of equal distribution of cases throughout the 4 seasons), the minimum change in odds ratio (OR) that could be detected was 2.4 (obtained by using a software program assuming Fleiss' calculation).[e] To detect smaller changes in OR, we could have included more SRMA cases. We could have allowed cases over 24 months of age (n = 2), those with other neurologic signs (n = 4), and those with mixed or mononuclear pleocytosis (n = 12) because these findings have been described previously with SRMA.[2] We were concerned that by including these cases we may have included other inflammatory meningioencephalitides.[1]

We conclude that only breed affected the odds of developing SRMA in this population of dogs in the South West United Kingdom. We cannot refute the possibility of other breeds being predisposed to SRMA. It is highly likely given the immune-mediated nature of SRMA that multiple factors contribute to the etiopathogenesis of the disease. This study has not excluded other tested or untested environmental, social, or demographic factors being involved in SRMA, but given its findings and the fact that previous studies have failed to identify infectious or neoplastic triggers for SRMA, it would seem prudent to investigate the genetics of the breeds with increased odds to try and elucidate the pathogenesis of SRMA. Such studies may lead to the development of a genetic test that could identify individuals susceptible to SRMA and allow a breeding program to eliminate SRMA if other treatable triggers are not discovered.

Footnotes

[a] Research Randomizer, version 4.0, Urbaniak, G. C., & Plous, S. (2013) [cited 2013, Jan 01] Available from: http://www.randomizer.org/

[b] Office for National Statistics, Postcode Directories. UK Data Service Census © Crown Copyright 2006

[c] IBM SPSS Statistics for Windows, version 19.0, IBM Corp, Armonk, NY,

[d] GraphPad Prism for Windows, version 5.00, GraphPad Software, San Diego, CA

[e] EpiInfo 7 for Windows, version 7.1.2, Centers for Disease Control and Prevention, Atlanta, GA

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Conflict of Interest: Authors disclose no conflict of interest.

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